UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
SHERMAN DIVISION

AMERICAN CLINICAL LABORATORY ASSOCIATION, ET AL. v. UNITED STATES FOOD AND DRUG ADMINISTRATION, ET AL.	CIVIL NO. 4:24-CV-479-SDJ
ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL. v. UNITED STATES FOOD AND DRUG ADMINISTRATION, ET AL.	CIVIL NO. 4:24-CV-824-SDJ

BRIEF OF AMICUS CURIAE CENTER FOR SCIENCE IN THE PUBLIC INTEREST IN SUPPORT OF DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT AND OPPOSITION TO PLAINTIFFS' MOTIONS FOR SUMMARY JUDMGENT

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Abbreviation	Meaning
ACLA	American Clinical Laboratories Association
AMP	Association for Molecular Pathology
CLEP	New York State Department of Health's Clinical Laboratory Evaluation Program
CLIA	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare & Medicaid Services
CSPI	Center for Science in the Public Interest
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
HHS	Department of Health and Human Services
IVDMIAs	In Vitro Diagnostic Multivariate Index Assays
IVDs	In Vitro Diagnostic Products or Tests
LDTs	Laboratory-Developed Tests
MAC	Medicare Administrative Contractor
MDA	Medical Device Amendments of 1976
MolDx	Molecular Diagnostic Program, administered by Palmetto
NIPTs	Non-Invasive Prenatal Tests

INTEREST OF *AMICUS CURIAE*

Amicus Center for Science in the Public Interest (CSPI) monitors the Food and Drug Administration (FDA) on behalf of consumers. Founded in 1971, CSPI has, for five decades, been one of the nation's leading non-profit consumer advocacy organizations, advancing its mission of improving public health by advocating for sound science-based policies and truthful advertising in the food, dietary supplement, drug, and medical device spaces. With independence and scientific rigor, CSPI works to reduce the impact and burden of preventable diseases.

Dr. Peter Lurie, CSPI's President and Executive Director, is a leading advocate for greater oversight of LDTs. In 2015, while Dr. Lurie was serving as Associate Commissioner for Public Health Strategy and Analysis at the FDA, he was the lead author of a published Case Study Report that identified 20 problematic LDTs that caused or may have caused significant harm to patients.[1]

As part of its broader mission, CSPI engages in public education and advocacy related to medical devices, including Laboratory-Developed Tests (LDTs). This body of work includes leading a coalition of over 20 organizations interested in LDT oversight, developing and disseminating information to CSPI's members and the public regarding LDTs and advocating for Congress and federal agencies to strengthen the regulation of LDTs, including through submission of comments on FDA's 2023 Proposed Rule, "Medical Devices; Laboratory Developed Tests," published at 88 Fed. Reg. 68006 (Proposed Rule).[2]

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[1] *See* FDA, *The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies* (2015). Available at: https://bit.ly/3Q2gBE1 (2015 FDA Report).

[2] *See, e.g.*, CSPI, *Fact Sheet: The Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2021* (2022). Available at: https://tinyurl.com/mr33ruab; CSPI *et al*. letter to Robert M. Califf, Commissioner, *FDA, Stakeholder Groups Urge the FDA to Pass Regulation on Laboratory-Developed Tests* (May 30, 2023). Available at: https://tinyurl.com/4wf8sadx; CSPI,

INTRODUCTION AND SUMMARY OF ARGUMENT

Plaintiffs – two industry groups with an economic interest in avoiding regulatory compliance costs - have filed suit to challenge FDA's Final Rule[3] amending its regulations to make explicit that a subset of "in vitro diagnostic" products or tests (IVDs) known as "laboratory-developed tests" (LDTs) are devices under the Federal Food, Drug, and Cosmetic Act (FDCA). While FDA has held the authority to regulate IVDs since Congress passed the Medical Device Amendments (MDA), which amended the FDCA in 1976, and has long exercised its regulatory authority to regulate large swaths of such tests, it had previously exercised enforcement discretion over the subset of IVDs offered as LDTs.[4]

Initially, such discretion was reasonable. Until recent years, IVDs offered as LDTs were used only for a small number of patients in special clinical circumstances, were often simple tests, were frequently employed within academic medical centers, and were developed based on the diagnostic expertise of a group of pathologists and clinicians working together.[5] Now, however, LDTs represent a $20 billion industry, with tens of thousands of complex tests being offered to millions of patients to diagnose and evaluate a wide range of conditions, from everyday illnesses to terminal cancers.[6]

Comment on Proposed Rule re: Medical Devices; Laboratory Developed Tests (Dec. 4, 2023). Available at: https://tinyurl.com/ybtrbkcs.

[3] "Final Rule" refers to FDA's 2024 Final Rule, "Medical Devices; Laboratory Developed Tests," published at 89 Fed. Reg. 37286 (May 6, 2024).

[4] CSPI defines IVDs offered as LDTs in the same way that FDA did in its Final Rule: "FDA uses the phrase 'IVDs offered as LDTs' throughout this preamble to refer to IVDs that are manufactured and offered as LDTs by laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and that meet the regulatory requirements under CLIA to perform high complexity testing, and used within such laboratories, even if those IVDs do not fall within FDA's traditional understanding of an LDT because they are not designed, manufactured, and used within a single laboratory." 89 Fed Reg. at 37365.

[5] *See* 88 Fed. Reg. 68009.

[6] *See* 89 Fed. Reg. at 37336-37340.

There is no doubt that Plaintiffs would like to see their rapidly advancing industry regulated with the same very limited oversight that FDA chose to exercise over LDTs when they were still a fledgling technology. However, in arguing that the Final Rule, which merely ends FDA's enforcement discretion over IVDs offered as LDTs, should be held invalid, Plaintiffs misconstrue the facts underpinning FDA's well-reasoned and valid decision to promulgate the Final Rule.

Plaintiffs ignore two important and inconvenient facts: (1) LDTs are a subset of IVDs and FDA has regulated IVDs for nearly 50 years without objection from the Plaintiffs; and (2) despite Plaintiffs' arguments that it would be unduly burdensome to subject them to regulatory oversight beyond CLIA,[7] for more than 30 years, Plaintiffs and other laboratories have complied with government oversight of IVDs in addition to CLIA's regulation of laboratories without issue. Further, Plaintiffs largely sidestep the central rationale for FDA's promulgation of the Final Rule: that greater oversight of LDTs is necessary to keep inaccurate tests off the market, and to avoid the adverse public health effects that result from those inaccurate tests.

This Brief provides a description of the relevant history concerning FDA's regulation of LDTs (both to provide history that Plaintiffs omit and to correct some of their misleading contentions); discusses the longstanding regulation of IVDs and the oversight of laboratories under CLIA and other laws; and addresses the present-day circumstances necessitating the Final Rule (both the inaccuracy of many LDTs and the adverse effects to public health that will occur if FDA is not permitted to exercise its authority to regulate this subset of IVDs).

[7] *See, e.g.,* ECF 27 at 19. "CLIA" refers to Clinical Laboratory Improvement Amendments of 1988.

ARGUMENT

I. Plaintiffs Mischaracterize the Relevant Legislative and Regulatory History.

Central to Plaintiffs' argument is their contention that the Final Rule represents a new and unprecedented assertion of authority by FDA. This is untrue. On the contrary, FDA has consistently issued guidance or made other public statements asserting its authority over IVDs, including LDTs, for nearly 50 years. Plaintiffs rely on misleading and cherry-picked historical statements that give an inaccurate picture of the true history that reveals that FDA has held and exercised regulatory authority over IVDs since 1976. More importantly, even Plaintiffs' skewed and incomplete version of the historical facts does not override the central, controlling factor in determining the validity of the Final Rule: that FDA is statutorily authorized under the FDCA as amended by the MDA to regulate IVDs, including LDTs.

A. LDTs are a subset of IVDs, which FDA has long regulated.

The challenge to FDA's Final Rule is based on a false assumption that FDA's assertion of its right to regulate LDTs has been "late-breaking and sporadic;"[8] in actuality, however, FDA has consistently maintained its authority over IVDs, including those offered as LDTs. As FDA notes throughout the Final Rule, LDTs are merely a subset of IVDs – a category of devices that the Agency has long regulated.[9] In fact, FDA has been clear since at least 1992 that LDTs are, by definition, IVDs, which it has the authority to regulate.[10]

The following summarizes FDA's key assertions of authority over IVDs:

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[8] ECF No. 20 at 10.

[9] FDA's authority to regulate these devices stems from sections 201(h)(1), 301, 501, 502, 510, 513, 514, 515, 518, 519, 520, 701, 702, 704, and 801 of the FDCA (21 U.S.C. §§ 321(h)(1), 331, 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 371, 372, 374, and 381) and section 351 of the Public Health Service Act (42 U.S.C. § 262). *See* 89 Fed. Reg. at 37287.

[10] 89 Fed. Reg. at 37328.

1. In 1972, FDA indicated its intent to regulate all IVDs, issuing a notice of intent to propose regulations.[11] In its description of IVDs in that notice, FDA did not distinguish IVDs offered as LDTs as a distinct category of tests to be regulated differently.[12]

2. In 1973, FDA proposed an IVD Rule, which defined the "in vitro diagnostic products" subject to regulation to include IVD test "systems intended for use in the diagnosis of disease."[13]

3. In subsequent years, leading up to the passage of the MDA in 1976, FDA garnered support for regulation of IVDs, including those offered as LDTs. In 1973, the College of American Pathologists suggested including diagnostic kits in the MDA.[14]

4. The first rulemaking implementing the MDA occurred in 1977. In that rulemaking, FDA recognized that laboratories may be considered device manufacturers subject to regulation, and provided only a limited exemption from registration and listing for those "clinical laborator[ies]" that primarily "provide a service through the use of a previously manufactured device."[15]

5. After the passage of the MDA, FDA worked to phase in a flexible regulatory framework for all devices, including IVDs.[16] In 1980, FDA continued promulgating rules regulating diagnostic tests under its newfound MDA authority.[17] FDA initially focused on IVDs in the "commercially distributed pathway," meaning test kits manufactured and assembled in a factory and shipped to multiple laboratories for use.[18] The other IVD pathway, IVDs offered as LDTs, were subject to enforcement discretion, a decision based on the overall low risk of these tests at the time.[19]

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[11] 37 Fed. Reg. 819 (Jan. 19, 1972).
[12] *Id*.
[13] 38 Fed. Reg. at 7098 § 167.1(a).
[14] Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare United States Senate, 93rd Cong., at 927-28 (1973) (Letter from William Reals).
[15] 42 Fed. Reg. 42520, 42528 (Aug. 23, 1977).
[16] FDA, *Public meeting on oversight of laboratory developed tests. Food and Drug Administration*, at 14-15 (July 19, 2010) (2010 Meeting Transcript). Available at: https://tinyurl.com/2h8ukdwz.
[17] *See* FDA, Final Rule: Classification of Electrophoretic Hemoglobin Analysis Systems, 45 Fed. Reg. 60619 (Sept. 12, 1980).
[18] 2010 Meeting Transcript, *supra* n. 16, at 17-18.
[19] *Id*. at 19. As publicly described by an FDA official, IVDs offered as LDTs were typically used in a small number of patients in special clinical circumstances, and developed based on the diagnostic expertise of a group of pathologists and clinicians. *Id*. at 21-22. According to that official, FDA has been clear that, "this choice does not change the fact that the law applies to those products. It really just changes the practical application of those laws and regulations." *Id*. at 20.

6. In the 1990s, technological advances, spurred in part by the Human Genome Project, led to the rapid proliferation of complex IVDs offered as LDTs.[20] This outpaced the availability of FDA-approved reagents for genetic testing, and laboratories relied on research-grade—not FDA-approved—reagents and instruments for testing.[21] The potential increased risks introduced in this era led to FDA's vocal reassertion of their authority and deliberate reassessment of how to mitigate such potential risks.[22]

7. Incrementally increased oversight of certain categories of IVDs offered as LDTs began in 1992 when FDA released a draft Compliance Policy Guide addressing the Commercialization of Unapproved IVD Devices Labeled for Research and Investigation. In it, FDA declared that IVDs offered as LDTs, which they called "home brew" products, manufactured by laboratories for diagnostic purposes "are subject to the same regulatory requirements as any unapproved medical device."[23]

8. In 1997, FDA released its Final Rule on Analyte Specific Reagents.[24] This rule, developed as an incremental step toward mitigating the potential risks of IVDs offered as LDTs, reclassified laboratory testing reagents, often used in LDTs, as devices and announced FDA's intent to regulate them in a manner consistent with its existing regulation of other tests.[25]

9. In 2006, FDA released a draft guidance regarding In Vitro Diagnostic Multivariate Index Assays (IVDMIAs), a subset of IVDs, often LDTs, that combined in vitro assays with algorithms for diagnostic purposes.[26] In the draft Guidance, FDA sought "to identify IVDMIAs as a discrete category of device, and to clarify that, even when offered as LDTs, IVDMIAs must meet pre- and post-market device requirements under the FDCA and FDA regulations,"[27] thus furthering its assertion that FDA's authority granted by FDCA reached at least some LDTs.[28]

10. FDA again publicly declared its authority over IVDs offered as LDTs in a 2010 public meeting specifically held to discuss oversight of LDTs.[29] FDA reiterated that it never relinquished its authority to regulate IVDs offered as LDTs, noting that despite its

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[20] *Id.* at 23.
[21] *Id*. at 24.
[22] *Id*. at 25-27.
[23] FDA, *DRAFT: Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation* (Aug. 3, 1992). Available at: https://tinyurl.com/5n6vccdr.
[24] "Analyte Specific Reagents" refers to biological molecules which are used to measure chemical substances; these reagents are a component of IVD tests. *See* FDA, *Overview of IVD Regulations* (Oct. 18, 2021). Available at: https://tinyurl.com/bddyrhdc.
[25] 62 Fed. Reg. 62243 (Nov. 21, 1997).
[26] 72 Fed. Reg. at 41082 (July 26, 2007).
[27] *Id*.
[28] We are aware of no distinction relevant to this proceeding between IVDMIAs and other LDTs, nor have Plaintiffs asserted such in their briefs.
[29] 2010 Meeting Transcript, *supra* n. 16 at 18-19.

historical practice of enforcement discretion, "[t]he law is in effect. We have simply, as a matter of policy, determined not to exercise or not to enforce that authority as of right now."[30]

11. In 2014, FDA put its long-held assertion into effect regarding IVDs offered as LDTs culminating in the Agency's 2014 draft guidance proposing oversight of LDTs. [31] The draft guidance reflected feedback from the 2010 public meeting.[32]

12. The 2014 draft guidance was followed by a public meeting in 2015,[33] and a 2015 report highlighting 20 potentially problematic LDTs (2015 FDA Report).[34] Each asserted that FDA has long had jurisdiction over IVDs offered as LDTs and was now seeking to phase out its enforcement discretion.

13. After the withdrawal of the draft guidance in 2017, FDA released a discussion paper summarizing the comments provided to it regarding the guidance and supporting a tailored regulatory path forward, given the growing need for oversight of these tests *(see infra* Section II.B., discussing adverse effects from unregulated LDTs).[35]

14. In more recent years, under both Democratic and Republican administrations, FDA has continued making public statements regarding IVDs offered as LDTs, the need for increased oversight, and FDA's authority to regulate such tests. For example, in 2018, former FDA Commissioner Scott Gottlieb, under Republican President Donald Trump, gave a speech regarding the importance of ensuring the safety and accuracy of these tests, particularly for cancer diagnosis and treatment.[36]

15. Plaintiffs[37] cite in detail the contents of a 2020 memorandum[38] from the then-General Counsel for the Department of Health and Human Services (HHS), Robert Charrow. While in the memorandum, Charrow questions FDA's authority over IVDs offered as

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[30] *Id.* at 113.
[31] 79 Fed. Reg. 59776 (Oct. 3, 2014).
[32] *Id*. at 59777.
[33] Notice of Public Meeting, 79 Fed. Reg. 69860 (Nov. 24, 2014).
[34] 2015 FDA Report, *supra* n. 2.
[35] FDA, *Discussion Paper on Laboratory Developed Tests (LDTs)* (Jan. 13, 2017). Available at: https://tinyurl.com/ycybx6uc (noting "FDA's 40-year experience in assuring the analytical and clinical validity of tests" and stating that "CMS's oversight of laboratories through CLIA is fundamentally different from FDA's oversight of the tests themselves.").
[36] Scott Gottlieb, *Blueprint for Breakthroughs – Charting the Course for Precision Medicine.* (Sept. 13, 2018). Available at: https://tinyurl.com/ymr2ztwr. ("[W]e should have a consistent approach for all in vitro clinical tests. Our approach needs to be the same whether the test developer is a traditional manufacturer or a clinical laboratory.").
[37] *See* ECF No. 20 at 12-13; ECF No. 27 at 16 –17.
[38] U.S. Dep't of Health and Human Services (HHS), *Federal Authority to Regulate Laboratory Developed Tests Memorandum* (June 22, 2020). Available at: https://tinyurl.com/mrk5ayct.

LDTs on a variety of grounds,[39] this reference in the Plaintiffs' briefs lacks relevant context. ACLA fails to note that the memorandum was publicly withdrawn on November 15, 2021, due in part to concerns about problematic IVDs offered as LDTs.[40] AMP's claim the withdrawal was a "transparently political decision" is irrelevant to FDA's authority to promulgate the Final Rule, and, even if accurate, is true of many agency policymaking decisions, and does not render those decisions inherently invalid. Moreover, a single memorandum – which was quickly retracted – does not contravene the decades of history described herein demonstrating FDA's authority to regulate IVDs.

16. In 2022, FDA, spurred, in part, by a letter from almost 100 Republican members of Congress,[41] issued a safety warning regarding non-invasive prenatal tests (NIPTs),[42] a common IVD category offered as an LDT to pregnant people. ***If Congress did not agree that FDA had authority over IVDs offered as LDTs, it would not have directed FDA to intervene when these problematic IVDs offered as LDTs came to light***. The FDA safety warning included warnings and precautions for patients and practitioners.[43]

Thus, FDA's public assertions of authority over IVDs date back to 1972, and the Agency has never suggested an intent to abdicate its authority over the subset of IVDs offered as LDTs. These public assertions of authority span decades and have occurred under administrations led by both major political parties. This depth of history can hardly be called "sporadic" or "late-breaking." Public statements in support of FDA's authority to oversee IVDs, including those offered as LDTs, are summarized in the table at **Exhibit A**.

B. There is no reason for LDTs to be regulated differently from other IVDs.

Although, prior to the FDA promulgating the Final Rule, LDTs were subject to different oversight than other IVDs, these tests rely on the same technology, are used for the same

[39] *Id.*
[40] HHS, *Statement by HHS Secretary Xavier Becerra on Withdrawal of HHS Policy on Laboratory-Developed Tests* (Nov. 15, 2021). Available at: https://tinyurl.com/288n47ej.
[41] Roy C. Daines *et al.*, *Letter from Congress to Commissioner Janet Woodcock* (Jan. 21, 2022). Available at: https://tinyurl.com/mr2phrk7.
[42] FDA, *Genetic Non-Invasive Prenatal Screening Tests May Have False Results: FDA Safety Communication* (April 19, 2022). Available at: https://tinyurl.com/5a4fdwkd,
[43] *Id.*

purposes, and are generally not distinguished by either patients or clinicians. A patient can provide a sample to a laboratory like Labcorp, which might then run an FDA-cleared or -approved test or use a test kit, thereby using IVDs approved by FDA. But in many cases, Labcorp might instead run a test that was developed in-house, or a modified version of an existing an IVD; both of these are LDTs. This is illustrated in **Exhibit B**. Despite testing for the same condition or biomarker, this second category of tests – LDTs – has ***not*** been subject to FDA approval. In both scenarios, the laboratory may be testing for the same condition, and the clinician and patient may be basing the same diagnosis and treatment decision on the results of the test. However, only in the case of FDA-regulated IVDs has the test been subject to prior FDA approval to ensure its accuracy.

The differences in regulatory oversight for the two types of tests - IVDs and the subset of IVDs offered as LDTs— are not based on any scientific, medical, or statutory rationale. As FDA explained in the Proposed Rule:

> In FDA's experience, including with COVID–19 tests and IVDs that are offered as LDTs after FDA's approval of a comparable companion diagnostic, many test systems made by laboratories today are functionally the same as those made by other manufacturers of IVDs. They involve the ***same materials and technologies***, are intended for the ***same or similar purposes, are developed by and for individuals with similar expertise***, and are ***marketed to the same patients***, sometimes on a national scale. For these reasons, ***tests made by laboratories are often used interchangeably by healthcare providers and patients with tests made by other manufacturers***.[44]

The graphic at **Exhibit B** illustrates that, in many cases, neither clinicians nor patients know whether the test used to make significant diagnoses and treatment decisions is an IVD, meeting FDA standards, or an IVD offered as an LDT, which has not been subject to those standards and might not be sufficiently accurate. The testing at these locations may be done with

[44] 88 Fed. Reg. 68006.

an FDA-approved IVD test kit, a modified FDA-approved IVD offered as an LDT (which would not have undergone FDA review), or an unapproved, in-house designed IVD offered as an LDT (which also would not be reviewed by FDA), a distinction that is neither clear to nor within the control of the patient or, likely, the clinician who ordered the test. A treating doctor, such as an oncologist, should not be tasked with determining the provenance, accuracy, or validity of the test result.

C. The historical record demonstrates that CLIA and FDCA serve complementary, rather than overlapping, purposes.

Based on a tortured and misleading reading of the legislative and regulatory history, Plaintiffs attempt to argue that IVDs offered as LDTs should be treated differently from other forms of IVDs. Such differential treatment, however, is not supported in the history Plaintiffs provide. Chiefly, Plaintiffs attempt to illustrate Congressional intent using a House report from the 1988 CLIA Amendments (more than a decade after the passage of the MDA), which states the "federal regulation of laboratories" falls "under two programs"—the Clinical Laboratories Improvement Act of 1967 and the Medicare statute—and did not mention regulation under the FDCA.[45] To the Plaintiffs, this apparently indicates that Congress did not intend FDA to regulate LDTs.

This argument is misleading and its significance exaggerated. First and foremost, this report language is unrelated to FDA's authority over IVDs, including LDTs, as it (and CLIA itself) addresses the regulation of *laboratories*, while FDA regulates laboratory *test*s—the

[45] ECF No. 20 at 9-10 (citing H.R. Rep. No. 100-899, at 11 (1988)); *see also* ECF No. 27 at 15.

products at issue in this litigation.[46] Second, of course, the lack of mention of FDCA in a House report discussing amendments to CLIA is immaterial to FDA's statutory authority.[47]

D. For more than 30 years, Plaintiffs and other laboratories have complied with additional oversight pathways without issue.

Even if, as Plaintiffs suggest, CLIA was intended to be the single regulatory mechanism for laboratories and their tests, that has never been the reality. The clinical laboratory regulatory scheme has consisted, and continues to consist, of multiple legislative enactments and oversight bodies, even before FDA introduced its Final Rule concerning IVDs offered as LDTs.

Since 1991, one form of oversight, in addition to CLIA, has been CLEP,[48] which provides for the oversight of laboratories and tests in the state of New York. The program requires enrollment for any laboratory that seeks to use samples from patients in New York State, regardless of where the test is performed.[49] Laboratories that have clinical laboratory permits from the New York program are exempt from CLIA.[50]

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[46] H.R. Rep. No. 100-899, at 12 (1988).

[47] From the same 1988 report, ACLA argues that "CLIA's purpose was to ensure that laboratory testing services are governed by a single 'unified regulatory mechanism." ECF No. 20 at 10. However, as the quoted language from ACLA's brief admits, the report was referring to the *laboratories*, not the *laboratory test*s themselves, as asserted by Plaintiffs. Such a *facility*, the report says, "[has] an effect on the public health and that each should be regulated under a unified regulatory mechanism." H.R. Rep. No. 100-899, at 12 (1988).

[48] "CLEP" refers to the New York State Department of Health Clinical Laboratory Evaluation Program.

[49] CLEP "seeks to ensure the accuracy and reliability of test results in clinical laboratories located in or accepting specimens from New York State (NYS) through on-site inspections, proficiency testing and evaluation of the qualifications of personnel of state permit-holding clinical laboratories and blood banks. The proper performance of diagnostic laboratory tests is a matter of vital concern, affecting the public health, safety and welfare of all NYS residents." New York State Department of Health, *About the Program.* Available at https://www.wadsworth.org/regulatory/clep/about-the-program.

[50] *See id.* ("The excellence of the center's Clinical Laboratory Evaluation Program has been acknowledged by CMS through their granting of exempt status from the federal Clinical Laboratory Improvement Amendments of 1988 for laboratories located in and holding NYS clinical laboratory permits.").

Another parallel oversight program, since 2011, is the Molecular Diagnostic Services Program (MolDX). In the absence of sufficient regulation of clinical validity of IVDs offered as LDTs, MolDx was created to ensure that Palmetto, a Medicare Administrative Contractor (MAC), pays for tests meeting the statutory requirement for reimbursement of "reasonable and necessary" items or services.[51] The program reviews non-FDA approved/cleared tests and modified FDA approved/cleared tests.[52] In total, Medicare beneficiaries in 26 states are benefitting from the program.[53] ***Plaintiffs, and the rest of the clinical laboratory industry, have complied with these additional oversight pathways over the last three decades and appear to raise no issues with the current regulatory regimen.***

Even setting these two programs aside, CLIA and FDCA now exist as complementary, rather than duplicative, regulatory schemes for laboratories and the tests they use, respectively, and this arrangement has been confirmed by both CMS and FDA. In 2013, CMS released a fact sheet in which it clearly delineated the balanced roles of CLIA and FDA in the oversight of IVDs offered as LDTs.[54] ***Significantly, CMS has repeatedly asserted, as recently as January 2024, that they do not have the expertise to regulate IVDs offered as LDTs.***[55]

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[51] *See* CMS, *MolDX: Molecular Diagnostic Tests*. Available at: https://tinyurl.com/4n6pj4cz.
[52] *Id*.
[53] "Although Palmetto 'owns' the MolDX program, several other MACs also participate in the program. These include Noridian JE and JF, CGS J15, and WPS J5 and J8." Medical Management Plus, *The Molecular Diagnostic Services (MolDX) Program*, (Nov. 17, 2017). Available at: https://tinyurl.com/3uxr3ada.
[54] The fact sheet noted that under CLIA, "analytical validation is limited, however, to the specific conditions, staff, equipment and patient population of the particular laboratory, so the findings of these laboratory-specific analytical validation are ***not meaningful outside of the laboratory that did the analysis***," whereas "FDA's premarket clearance and approval processes assess the analytical validity of a test system in greater depth and scope." CMS, *LDT and CLIA FAQs* (2013) (emphasis added). Available at: https://tinyurl.com/3xn6y6k7.
[55] Jeff Shuren and Dora Hughes, *FDA and CMS: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made,* FDA (Jan. 18, 2024). Available at: https://tinyurl.com/bd9z582t.

Despite the fact that FDA has, for nearly 50 years, claimed the authority to regulate laboratory testing and that CMS has expressly stated that it does not have the expertise to do so, Plaintiffs nevertheless insist that both agencies have, for decades, been ***wrong*** about their authority, and that Congress's unspoken intent was to create a fragmented regulatory scheme where FDA is permitted to regulate only certain diagnostic tests (IVDs not offered as LDTs), while LDTs would be subject to regulation only by a body that admits it lacks the capacity to do so. This would be a convenient outcome for industry groups, but it is nevertheless a nonsensical one.

The complementary nature of FDCA and CLIA is illustrated by what CLIA does not cover. Assuring the accuracy of LDT test results by regulating the testing procedures is the responsibility of CLIA; assessing that LDT tests are a clinically valid diagnostic tool is a role played solely by FDA.[56] CLIA does ***not*** ensure a number of test aspects, including: safety and effectiveness of LDTs prior to marketing; quality and design of devices; adequate labeling for directions for use; truth in marketing; adverse event reporting; removal of unsafe tests; and human subjects protections for clinical studies using LDTs.[57]

As CMS agrees, these are the responsibilities of FDA. Relying on CLIA oversight alone is insufficient to assure the performance of all elements that go into testing. The Final Rule is a step toward that vision and toward achieving the comprehensive oversight of both laboratories *and* their tests that Congress intended.

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[56] *See* Jonathan R. Genzen *et al.*, *Laboratory-Developed Tests: A Legislative and Regulatory Review*, 63 CLINICAL CHEMISTRY 1575 (Oct. 1, 2017).
[57] *See* 2015 FDA Report, *supra* n. 1.

E. FDA's statutory authority over IVDs, including those offered as LDTs, comes from FDCA, and other historical statements are ultimately irrelevant.

As noted, FDA was directed to regulate IVDs offered as LDTs in the FDCA as amended by the MDA.[58] Plaintiffs attempt to undermine FDA's statutory authority by selectively highlighting legislative and regulatory history, as discussed *supra* Section I.C. Yet, the United States Supreme Court has been clear that "legislative history… is meant to clear up ambiguity, not create it."[59] In 2020, the Supreme Court reiterated this: "when the express terms of a statute give us one answer and extratextual considerations suggest another, it's no contest. Only the written word is the law."[60] Therefore, the words of the MDA are what ultimately determine FDA's authority. In this case, the MDA is clear in its device definition that FDA has authority over "in vitro reagent[s], or other similar or related article[s]."[61]

Flexibility in adopting new rules is not only permissible, but is a foundational element of effective agency administration. As the Supreme Court explained in *SEC v. Chenery*:

> [P]roblems may arise in a case which the administrative agency could not reasonably foresee, problems which must be solved despite the absence of a relevant general rule… In those situations, the agency must retain power to deal with the problems on a case-to-case basis if the administrative process is to be effective .... [a]nd ***the choice made between proceeding by general rule or by individual, ad hoc litigation is one that lies primarily in the informed discretion of the administrative agency***.[62]

The case of IVDs offered as LDTs is precisely the type of evolving issue that requires this type of informed agency action. The mere fact that FDA had not previously chosen to exercise its authority over these tests does not, as a matter of law, mean that they somehow have

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[58] See s*upra* n. 9.
[59] *Milner v. Dep't of Navy*, 562 U.S. 562, 574 (2011).
[60] *Bostock v. Clayton Cnty*., 590 U.S. 644, 653 (2020).
[61] 21 U.S.C. § 321(h)(1) (defining "device").
[62] *SEC v. Chenery*, 332 U.S. 194, 202-03 (1947) (emphasis added).

forfeited their ability to do so.[63] Rather, the power to regulate IVDs offered as LDTs remains soundly committed to FDA by statute, and the emergence of LDT technology has necessitated a different regulatory approach by the Agency – an approach reflected in the Final Rule and permitted by the Supreme Court in *SEC v. Chenery*.

II. FDA Oversight of LDTs Is Necessary to Ensure Accuracy and Prevent Adverse Effects.

A. Oversight of LDTs would ensure that inaccurate tests are identified.

At its core, in an effort to protect public health, the Final Rule simply seeks to ensure that LDTs are subject to the same rules as other IVDs already covered by FDA's regulations. Under the current scheme, IVDs, unless exempt, must follow FDA processes designed to ensure both ***analytical validity*** (*i.e.*, the test measures what it is supposed to measure) and ***clinical validity*** (*i.e.,* what the test measures is supported by rigorous scientific evidence for diagnosis and/or treatment). In contrast, under FDA's enforcement discretion, IVDs offered as LDTs have been subject only to CLIA regulation, which as FDA and CMS have together pointed out, includes an assessment of analytical, but not clinical, validity. These tests are often used for the same purposes, but they have been regulated differently, despite the fact that LDTs may, in fact, prove ***less*** accurate than their more heavily-regulated counterparts.[64]

Empirical research has shown that varying test performance between LDTs and other IVDs is not just a theoretical concern.[65] In a 2022 study in which laboratories tested standardized samples for genetic variants using their own LDTs, only seven of 19 (37%) laboratories correctly

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[63] *See id.*
[64] *See* Shuren and Hughes, *supra* n. 55.
[65] 88 Fed. Reg. at 68010-11; John D. Pfeiffer *et al.*, *Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics*, 157 AM. J. CLINICAL PATHOLOGY 628 (Apr. 1, 2022).

identified all variants.[66] Meanwhile, for a comparison, an FDA-approved IVD correctly reported all standardized variants.[67]

FDA's own experience reviewing certain IVDs offered as LDTs has further borne out these concerns. Although FDA has not enforced requirements for LDTs, it has received some premarket review submissions, investigational use submissions, and Emergency Use Authorization (EUA) requests for LDTs from laboratories acting as test manufacturers.[68] Through these submissions concerning tests for serious diseases and conditions such as Alzheimer's Disease, heart disease, and blood cancer, FDA notes that it "has observed that many laboratories fail to perform appropriate or adequate validation studies, have data demonstrating their test does not work as intended but offer the test anyway, or use instruments and other components that are not adequately controlled for clinical use."[69]

B. Inaccurate testing by LDTs has adverse effects on public health.

The fact that certain IVDs offered as LDTs have been shown to be less accurate is a critical rationale for the Final Rule, as inaccurate testing poses a real-world threat to public health. As FDA noted in its Proposed Rule, it has, for years, been attempting to track the adverse impacts of LDT inaccuracy, including in its 2015 Report.[70] Recent evidence from various sources, including numerous peer-reviewed scientific studies,[71] demonstrates that the risks

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[66] *Id*.
[67] *See supra* n. 65.
[68] 88 Fed. Reg. at 68011.
[69] EUA requests for COVID-19 molecular diagnostic tests, for example, showed that of the first 125 EUA requests received from laboratories, 82 showed test design or validation problems. *Id*.
[70] 88 Fed. Reg. 68006.
[71] FDA cites several examples of recent studies and articles demonstrating the fallability of LDTs in its Proposed Rule. For example, in one study testing standardized samples for genetic variants, only seven of 19 laboratories correctly identified all variants. In another study, an LDT claiming to offer early cancer detection tests, delivered nine false positive results for every true cancer diagnosis. *See supra* n. 65.

associated with LDTs may only be getting worse.[72] Overall, FDA notes that the evidence points to "fundamental uncertainty in the marketplace about whether the IVDs offered as LDTs provide accurate and reliable results."

Inaccurate testing results are unfortunately common and can have significant adverse effects. As FDA states in the Preamble to the Final Rule, "[t]oday's LDTs are also more commonly manufactured with instruments or other components not legally marketed for clinical use and are ***more often used to inform or direct critical treatment decisions, to widely screen for common diseases, to predict personal risk of developing certain diseases, and to diagnose serious medical conditions such as cancer and heart disease***."[73]

Given that LDTs can be used for these highly consequential purposes, the risks of an inaccurate result may be grave: with a false negative test (a disease or condition is not detected when it is actually present), patients may fail to obtain necessary treatment which could resolve or improve their condition. With a false positive (the test result signifies that a disease or condition is present when it actually is not), the patients may undergo procedures for conditions they do not have, which may be costly, intrusive, and harmful.[74]

Examples of such adverse effects caused by false results are well-documented.[75] In the 2015 FDA Report, which was compiled by FDA based solely on public information, the Agency detailed 20 examples of LDTs that either demonstrably harmed or may have harmed patients via inaccurate results.[76] For example:

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[72] 88 Fed. Reg. at 68010; 89 Fed. Reg. at 37381.
[73] 89 Fed. Reg. at 37289.
[74] *See, e.g., Id.* at 37327, 37296; *see also* 2015 FDA Report, *supra* n. 1 (discussing consequences of false negative and false positive results from LDTs).
[75] *See* 2015 FDA Report, *supra* n. 1 (detailing case studies from public sources involving adverse consequences from LDTs).
[76] *Id*.

1. Concerning false negatives, a test for predictors of breast cancer was found to ***miss key markers for cancer progression in more than a third of studied cases***, leading to multiple documented examples of patients experiencing significant cancer progression as a result of not obtaining earlier preventative treatment. Certain non-FDA approved LDTs for detecting high-risk HPV strains associated with cervical cancer were also found to produce false negatives.[77]

2. Concerning false positives, the 2015 FDA Report identified three separate LDTs that purported to accurately diagnose or predict ovarian cancer, but were actually prone to false positives.[78] One of these tests purported to accurately predict whether a patient was at high risk for ovarian cancer, claiming to be ">99.9% accurate," despite a lack of scientific evidence that the biomarker for which it tested was actually positively associated with ovarian cancer risk.[79] In extreme cases, these tests could lead to unnecessary surgical removal of the ovaries,[80] which can impose significant financial, medical, and psychosocial costs on the patient.[81] Other false positives concerned Lyme Disease and pertussis.[82]

Recent high-profile examples have demonstrated that accuracy rates for many LDTs, covering a range of different kinds of tests, can be low. One example is the blood-testing startup Theranos, which shut down and its executives were criminally convicted after years of investigative reporting and government investigations revealed that its highly touted LDT diagnostics were often not capable of yielding accurate results.[83] Theranos had for years made false representations about, and offered, tests for a multitude of health metrics and conditions,

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[77] *Id*. at 14-16.
[78] *Id*. at 9-12.
[79] *Id*. at 14-15.
[80] In fact, removal of the ovaries can lead to an increased risk of heart attack, lower bone density, Parkinson's and Alzheimer's Disease, among other problems. William H. Parker *et al.*, *Effect of Bilateral Oophorectomy on Women's Long-Term Health*, 5 WOMEN'S HEALTH 565 (2009).
[81] Adverse patient effects also impose costs on society and the healthcare system that can quickly become significant. For example, according to the 2015 FDA Report, each false negative result on the breast cancer screening test cited above imposed an average social cost of $775,238. *See* 2015 FDA Report.
[82] *Id*. at 8-13.
[83] *See* John Gilmore, *The Wild, Wild West of Laboratory Developed Tests*, 81 WASHINGTON & LEE L. REV. 259 (2024).

ranging from cholesterol level checks to cancer diagnoses, servicing hundreds of thousands of patients, performing millions of tests, all without any oversight from FDA.[84]

Another example of LDTs marketed to the public with only limited regulatory oversight and extremely low accuracy rates is NIPTs. Recent data collected and published by *The New York Times* revealed extremely low predictive value in neonatal testing for potential genetic defects. This data showed that, on tests for six rare conditions, positive results **are *inaccurate about 85 percent of the time*.**[85] Such results can have serious impacts on expectant parents, as they may lead to invasive and costly follow-up testing, or may even impact their decision regarding whether to carry a pregnancy to term.[86]

Despite these clear social costs, Plaintiffs suggest that the Final Rule is not adequately justified, contending that FDA has cited only a limited number of instances of problematic LDTs and characterizing the Agency's concerns about adverse events as "anecdotal."[87] This misses the point. Because adverse events involving LDTs are ***not*** required to be reported to FDA under the current regulatory scheme, FDA's database of device adverse effects likely only represents the "tip of the iceberg" when it comes to adverse consequences of LDT under-regulation. To the extent that they are anecdotal, that is due to the fact that under the enforcement discretion policy, the agency is not informed that new or modified tests will be marketed, nor are the companies

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[84] *Id*. at 260-64. *See also* John Carreyrou, *Hot Startup Theranos Has Struggled With its Blood-Test Technology*, WALL ST. J. (Oct. 16, 2015), https://tinyurl.com/ybujfc3j.
[85] *See* Sarah Kliff and Aatish Bhatia, *When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong*, N.Y. TIMES (Jan. 1, 2022).
[86] The Proposed Rule discusses some of the litigation that has been filed by consumers, shareholders, and investors about test efficacy, including about the neonatal tests. *See* 88 Fed. Reg. at 68012.
[87] ECF No. 27 at 38; *see also* ECF No. 20 at 38-39.

making these tests required to submit the adverse events associated with these tests to the agency.[88]

FDA's Final Rule strives to address this important issue by subjecting LDTs to the same requirements as other IVDs, including registration (companies must inform FDA that they make LDTs), listing (companies must inform FDA of the LDTs they are making), and adverse event reporting, which will help FDA identify further issues with LDTs being offered on the market. Subjecting LDTs to these requirements will result in more accurate tests, which cause fewer adverse effects for patients and promote accurate diagnoses and appropriate treatment more generally.

CONCLUSION

In light of the foregoing, as well as the arguments made by FDA and by other *amici* submitted on behalf of FDA, CSPI respectfully requests that this Court reject Plaintiffs' challenges to the Final Rule and enter summary judgment in favor of FDA.

Date: November 4, 2024

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[88] Of course, in addition to those adverse events, FDA is aware of the documented LDT adverse effects reflected in the scientific, peer-reviewed literature, several examples of which are cited in the preamble to the Final Rule. *See* 89 Fed. Reg. at 37289-93.

CERTIFICATE OF SERVICE

I hereby certify that on November 4, 2024, I caused the foregoing to be filed with the Clerk of the Court through the Court's ECF system, which will serve notice of the filing on all filers registered in the case.

/s/ *Lisa S. Mankofsky*
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